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**Introduction:** Alzheimer's disease (AD) is a neurodegerative disease caused by excessive production of amyloid beta (Aβ) peptide in neuronal cells. Beta site amyloid preursor protein cleavingenzyme 1 (BACE1) has been known as a key regulator of Aβ production. Recently, there is accumulating evidence that the risk of AD occurence is associated with diabetic mellitus representng high glucose concentration in blood plasma. However, the relationship with high glucose and BACE1-mediated Aβ secretion remains unclear. We aimed to investigate the effect of high glucose on BACE1 expression and related mechanism in vivo and in vitro.

**Materials and Methods:** We incubated SK-N-MC and treated 25mM of glucose. We performed cell viability assay, flow cytometry analysis, PCR, immunocytochemistry, immunoprecipitation immunohistochemistry by using ZLC, ZDF rat animal model

**Results:** In our results, using ZLC and ZDF rat models, we presented ZDF has high levels of Aβ and hyper-phosphorylated tau as well as BACE1 and APP-C99. To demonstrate the signaling pathway in vitro, we treated high dose of D-glucose to SK-N-MC neuronal cell model. We found that high glucose stimulated Aβ secretion in medium and neuronal cell apoptosis in a dose-dependent manner. In addition, we showed high glucose increased BACE1 and APP-C99 expressions, which are reversed by pretreatments of reactive oxygen species (ROS) scavenger NAC. High glucose induced intra-cellular ROS level and HIF-1α expression. Furthermore, we found high glucose reduced formation of RXR/LXR complex and stimulated RXR nuclear translcation in SK-N-MC cells, which is associated with regulation of BACE1 and ABCA1 expression. High glucose-induced ABCA1 down-regulation was recovered byTO901317 pretreatment. Furthermore, we showed high glucose sitmulatedintra-cellular cholesterol accumulation and lipid raft modification. Lipid raft disruption by MβCD pretreatment decreased BACE1 expression on the lipid raft and Aβ production. And, we confirmed silencing of BACE1 expression by small interfering RNA transfection regulated Aβ secretion, caspase 3/9 cleavage and apoptosis in SK-N-MC cells.

**Conclusions:** We demonstrated that high glucose stimulated BACE1 expression on lipid raft via ROS-induced RXR-ABCA1 pathway in SK-N-MC cells

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## Palmitic Acid Increased the Amyloid-β Secretion in SK-N-MC via GPR40-Mediated APP and BACE1 Upregulation

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**Introduction:** There are accumulating evidence that the patients with metabolic disease such as obesity representing high concentration of free fatty acid (FFA), for instance palmitic acid (PA), in the blood are susceptible to Alzheimer's disease (AD). Amyloid-β (Aβ), the key molecule inducing neuronal cell death and hyperphosphorylation of tau on AD patients, is a toxic protein that produced from amyloid precursor protein (APP) cleaving by BACE1. The aim of our study is to investigate the specific mechanism how PA regulates Aβsecretion, which can connect between obesity and AD occurrence.

**Materials and Methods:** We incubated SK-N-MC in DMEM with 50μM of PA invarious condition. 5-week-old male C57BL/6 mice were fed either a regular chow(RC) diet or 60% high fat diet for 8 weeks. In addition, we analyzed the effect of PA by using western blot, PCR, immunocytochemistry, and immunoprecipitation in the cell, and effect of HFD using immunohistochemistry and western blot in an obese mouse model.

**Results:** In an obese mouse model, high fat diet (HFD) significantly increased the expression of APP and BACE1, tau hyperphosphorylation, and Aβ secretion in the hippocampus and cortex. Thus, we examined the functional role of PA, as a representative FFA, in Aβ production in SK-N-MC neuroblastoma cells. APP and BACE1 were upregulated by PA in a time and dose-dependent manner, which were blocked by G-protein coupled receptor 40 (GPR40) inhibitor.PA-bound GPR40 stimulated AKT activation and phosphorylated mTOR and p70S6K1 that are responsible for activation and nuclear translocation of HIF1 α. On the other hand, PA also increased nuclear translocation of phosphorylated NF-κB via AKT activation. PA significantly enhanced the transcriptional activity of HIF1α and NF-κB on promoter region of APP and BACE1 genes. In addition, silencing of HIF1α and NF-κB inhibited the level of a catalytic product of APP, C99 fragment, in PA-treated SK-N-MC. Consistently, knock-down of APP and BACE1 decreased the production of Aβ.

**Conclusions:** PA, coupled with GPR40, induces over-production of Aβ by increasing APP and BACE1 via AKT-mTOR-HIF1α and AKT-NF-κB signaling pathway in SK-N-MC.

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## Hepatoprotective effects of allyl isothiocyanate in CCl4-induced chronic hepatic damage in rats

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